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# Early movement restriction impairs the development of sensorimotor integration, motor skills and memory in rats: Towards a preclinical model of developmental coordination disorder?

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## Abstract

Children with neurodevelopmental disorders, such as developmental coordination disorder (DCD), exhibit gross to fine sensorimotor impairments, reduced physical activity and interactions with the environment and people. This disorder co-exists with cognitive deficits, executive dysfunctions and learning impairments. Previously, we demonstrated in rats that limited amounts and atypical patterns of movements and somatosensory feedback during early movement restriction manifested in adulthood as degraded postural and locomotor abilities, and musculoskeletal histopathology, including muscle atrophy, hyperexcitability within sensorimotor circuitry and maladaptive cortical plasticity, leading to functional disorganization of the primary

**Abbreviations:** ADHD, attention deficit and hyperactivity disorder; ASD, autism spectrum disorder; DCD, developmental coordination disorder; P2, postnatal day 2; SMR, sensorimotor restriction.

Hanane Khalki, Diego Cabral Lacerda, Corane Karoutchi, Maxime Delcour, and Orlane Dupuis equal contributions.

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somatosensory and motor cortices in the absence of cortical histopathology. In this study, we asked how this developmental sensorimotor restriction (SMR) started to impact the integration of multisensory information and the emergence of sensorimotor reflexes in rats. We also questioned the enduring impact of SMR on motor activities, pain and memory. SMR led to deficits in the emergence of swimming and sensorimotor reflexes, the development of pain and altered locomotor patterns and posture with toe-walking, adult motor performance and night spontaneous activity. In addition, SMR induced exploratory hyperactivity, short-term impairments in object-recognition tasks and long-term deficits in object-location tasks. SMR rats displayed minor alterations in histological features of the hippocampus, entorhinal, perirhinal and postrhinal cortices yet no obvious changes in the prefrontal cortex. Taken all together, these results show similarities with the symptoms observed in children with DCD, although further exploration seems required to postulate whether developmental SMR corresponds to a rat model of DCD.

**KEYWORDS**

animal model, behavior, electrophysiology, neurodevelopmental disorders, neuromuscular

**1 | INTRODUCTION**

About 5–6% of age-school children have developmental coordination disorder (DCD), a neurodevelopmental disorder corresponding mainly to motor impairment ranging from gross to fine skill deficits that interfere with daily social and academic activities. DCD persists into adulthood in 30 to 70% of early detected cases and mainly affects males with a ratio ranging from 2 to 1 to 4–1 (Biotteau et al., 2020; Brown-Lum et al., 2020; Smits-Engelsman et al., 2020; Vaivre-Douret et al., 2016; Zwicker et al., 2012). Without apparent brain damage, but altered white matter ultrastructure and organization in the sensorimotor networks (Brown-Lum et al., 2020; Wilson et al., 2017), patients with DCD show reduced abilities in producing consistent movements, poor motor coordination and kinaesthetic acuity, broad impairments in sensorimotor representations and perception - each reflecting disrupted central networks (Coleman et al., 2001; Du et al., 2015; Gabbard & Bobbio, 2011; Kashuk et al., 2017; Vaivre-Douret et al., 2016; Zwicker et al., 2012). DCD usually co-occurs with one or more other neurodevelopmental disorders, such as attention deficit and hyperactivity disorder (ADHD), specific language impairment, learning and memory deficits, autism spectrum disorder (ASD), developmental dyslexia, dysgraphia, altered executive functions and/or psychiatric disorders (Biotteau et al., 2020; Gomez & Sirigu, 2015; Paquet et al., 2019; Smits-Engelsman et al., 2020; Vaivre-Douret et al., 2016; Zwicker et al., 2012). For instance,

children with ASD or ADHD exhibit gross or fine motor abnormalities, motor learning deficiencies and difficulties executing sequences of actions likely related to deficits in the internal model (Arango-Tobón et al., 2023; Chinello et al., 2016; Smits-Engelsman et al., 2020).

Overall, most children with DCD, ADHD or ASD show sensorimotor impairments, reduced physical activity, altered interactions with their environment and atypical motor development (Paquet et al., 2019). The latter is usually detected as atypical spontaneous or general movements in patients with motor impairment (Einspieler et al., 2016; Hadders-Algra, 2018; Phagava et al., 2008; Vaivre-Douret et al., 2016; Zuk, 2011). Atypical general movements correspond to rigid and cramped-synchronized and stereotyped movements that exhibit limited fluency, variation and complexity with increasing age, compared to typical ones. Atypical, disturbed general movements appear to reflect impaired connectivity and functional organization of the brain (Einspieler et al., 2014; Hadders-Algra, 2018; Zuk, 2011). Thus, we postulated that limited amounts and abnormal patterns of somatosensory inputs during development may lead to abnormal locomotion and maladaptive plasticity in the sensorimotor cortex.

To reproduce atypical motor development as can be observed in DCD, we developed a rodent model based on hind limb movement restriction from birth to 1 month of age that provides limited and atypical somatosensory feedback to the developing brain. This early sensorimotor restriction (SMR) mainly induced enduring movement

disorders, including reduced length and height of the swing, increased foot velocities and joint angles. These movement disorders that persist into adulthood are related to hyperextension of the knee and ankle, corresponding to a digitigrade locomotion that recapitulates “toe walking” or true pes equinus (Delcour, Massicotte, et al., 2018), a symptom frequently observed in patients with ASD (Vilensky et al., 1981) and cerebral palsy (Rodda et al., 2004). SMR also leads to a degradation of the functional organization and neuronal properties in both the primary somatosensory and motor cortices, along with hyperexcitability in the sensorimotor cortex and lumbar spinal cord, indicative of hyperreflexia, spasms and spasticity (Coq et al., 2020; Delcour, Massicotte, et al., 2018; Delcour, Russier, et al., 2018; Strata et al., 2004).

Sensorimotor disabilities that interfere with daily living activities and social interactions have been evidenced to alter the development of cognition and executive functions in children with DCD (Biotteau et al., 2020; Smits-Engelsman et al., 2020; Vaivre-Douret et al., 2016). Indeed, bodily experience and sensorimotor systems are crucial in human cognition to represent and recall objects and events (Eigsti et al., 2015). Thus, we hypothesized in the present study that limited and abnormal somatosensory inputs during development may lead in addition to sensorimotor disturbances to the disruption of early and enduring abilities to process and integrate sensorimotor and multisensory information so that the development of sensorimotor reflexes and social interactions would be impaired during SMR, as well as general activity levels, pain and object recognition memory in adult rats. To further explore these premises, we investigated here the impact of early SMR on the development of sensorimotor reflexes, such as cliff avoidance, surface righting reflex, negative geotaxis and swimming development and jumping down with choice to assess the abilities of SMR pups to integrate sensorimotor and multisensory inputs and to make choices based on social familiarity. We also tested the development of early sensorimotor abilities and strategies for locomotion, using the catwalk system at postnatal day 21 (P21). Then, we examined the general activity levels of adult SMR rats in the open-field and the actimetry cage, SMR-related changes in sensitivity for pain and abilities in non-spatial and spatial object memory tasks, as well as the histopathology in the related cortical areas, such as the parahippocampal complex and the prefrontal cortex. To assess a possible correspondence between symptoms in our SMR model and in children with DCD, ADHD or ASD, we investigated the development of motor and non-motor skills with our rat model of SMR, based on functional restriction of movement. Our SMR model differs from the genetic model of DCD based on

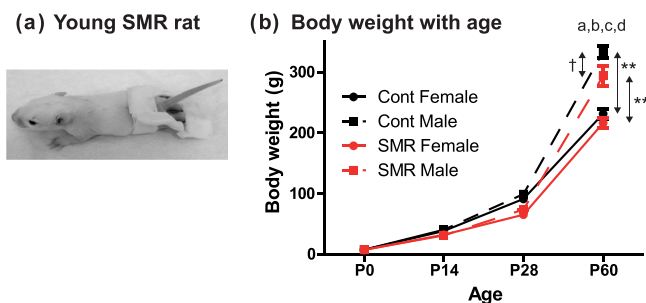
recombinant inbred mice lines that reproduce deficits in motor skills and learning (Gill et al., 2020) and from lesional or genetic models of ASD (e.g., Al Sagheer et al., 2018; Haida et al., 2019).

## 2 | MATERIALS AND METHODS

All experimental procedures and animal use have been carried out in accordance with the ARRIVE guidelines laid down by NIH (NIH Publication #80–23) and EU Directive (2010/63/EU), and approved by the local and national committees of ethics in Marseille (authorization APAFIS#20829–2019051718013359) and Lille (APAFIS#2021–020818231865).

### 2.1 | Animals and SMR

Rat pups of either sex from different litters of Sprague–Dawley and Wistar females were assigned to two groups: 1) a group subjected to transient hind limb immobilization from P1 to P28 for 16 hours per day, thus producing sensorimotor restriction (SMR), 2) a control group (Cont). The feet of the SMR pups were first gently bound together with medical tape. Their hind limbs were then immobilized in the extended position and taped to a cast, made of hand-moldable epoxy putty sticks (Figure 1a). These casts were well tolerated by the pups and mothers and allowed the pups to move at the hip, urinate,



**FIGURE 1** (a) Young rat exposed to postnatal hind limb immobilization resulting in sensorimotor restriction (SMR). The feet of the pup were tied together and attached with medical tape to a rigid cast made of epoxy stick. The hip joint was free to move compared to the knee, ankle and toes that remained in extended position for 16 hours a day of casting from P1 to P28. (b) Although there was significant effects of group and sex on body weight, post hoc comparisons did not indicate significant differences at birth, P14 and P28. At P60, males weighed more than females in the two groups and SMR males tended to weigh less than control males. a, significant effect of group; b, significant effect of sex; c, effect of age; significant interaction between factors; †, tendency,  $p < 0.06$ .

defecate and to receive maternal care. After casting, pups were returned to their mother and unrestrained littermates for 16 h mostly during the night phase, corresponding to daily peaks of motor activity. During the light phase, the casts were removed so that pups could move freely for 8 h/day. After daily uncasting, the hind limb joints were passively moved through their full range of motion. The size of the casts was adapted to the growth of the rats from P1 to P28. The casting was simulated in control rats without taping their hind limbs so that all rats received comparable handling. The possible impact of stress induced by the casting and hind limb immobilization was minimized by similar handling of all rats (Strata et al., 2004). After weaning on P28, rats of the same sex were housed by 3 in standard plastic cages (26.5 × 42.5 × 18 cm) with sawdust on the floor and objects. The cages were kept in a room with controlled temperature and humidity, 12-h light–dark cycles (8:00 am to 8:00 pm), and food and water ad libitum.

We used a total amount of 61 SMR (29 females and 32 males) and 69 control rats (36 females and 33 males) whose age ranged from P5 to P60 for behavioral tests and P60–90 for histology. Most of the rats performed several behavioral tests when compatible at different ages. All behavioral evaluations were performed at the beginning of the light phase 1–2 hours after cast removal and did not require food deprivation.

## 2.2 | Cliff avoidance

Each pup was placed on a table edge with the forepaws and head over the edge (Altman & Sudarshan, 1975). The amount of time required to complete backing and turning away from the cliff was recorded once at P5. The animals were tested for a maximum of 90 sec. We used 12 control and 15 SMR pups.

## 2.3 | Surface righting reflex

Each pup was placed on its back on a flat surface. The latency to regain all four paws in contact with the surface was recorded at P5, P7 and P13 with video. The maximum time allowed per trial was 30 sec (Altman & Sudarshan, 1975). We used 13 control and 16 SMR rats from P5 to P13.

## 2.4 | Negative geotaxis

Eighteen control and 14 SMR pups were placed head-down on a grip surface (silicon-made mesh) inclined 45°

(Altman & Sudarshan, 1975). The latency (sec) required to turn to 90° and subsequently to 180° was recorded. The animals were tested for a maximum time of 90 sec at P7, P9 and P13 and videotaped.

## 2.5 | Swimming development

This procedure has been described elsewhere (Khalki et al., 2012) and was adapted from prior studies (Altman & Sudarshan, 1975; Cazalets et al., 1990). Each rat was individually placed in a tank of water (28°C) for 10 sec and direction, angle in the water (head position) and limb usage were observed in the same animals at P10, P12 and P21. Direction scores consisted of sinking (0 points), floating (1), circling (2) and swimming straight or nearly straight (3). Angle scores consisted of head submerged (0), nose at the surface (1), nose and top of head at or above the surface but ears still below the surface (2), half of ears was above the surface (3) and ears completely above the surface (4). Limb use scores consisted of no paddling (0), paddling with all four limbs (1) and paddling with hind limbs only while stationary forelimbs (2). We pooled all the scores together to ease clarity. We used 13 control and 17 SMR rats from P10 to P21.

## 2.6 | Jumping down with choice

Each pup was placed on an elevated platform situated 20 cm above two cages; one containing siblings and the other one contained only sawdust (Altman & Sudarshan, 1975). The time to jump down into one of the cages as well as the choice was recorded at P15 and P17. The maximal duration of this test was 120 sec. We used 11 control and 12 SMR rat.

## 2.7 | Footprints and locomotion kinematics

To assess kinematics and patterns of locomotion, 9 control and 8 SMR rats at P21 were allowed to freely run across an illuminated glass walkway floor located in a corridor (width: 5 cm; length: 100 cm) of the Catwalk system (Noldus, Wageningen, The Netherlands). The footprints were digitized with a high-speed camera (10 frames.sec<sup>-1</sup>). For each rat, the length and duration of the stride, duration of the stance and swing, base of support (i.e., average width between either forelimbs or hind limbs), duty cycle (i.e., duration of stance divided by durations of stance and swing expressed in



percentage), maximal contact area ( $\text{mm}^2$ ) of each paw during stance, maximal weight load (i.e., maximal intensity at the maximal footprint area) and the mean angle of the paw line (drawn manually from the middle of the third toe/finger to the heel or between palmar pads) with the body axis were automatically computed using the Catwalk system as rats crossed the walkway without any interruption or hitch during each of the three required run (Delcour, Massicotte, et al., 2018). Locomotion patterns correspond to the order in which the paws were placed on the glass walkway with predefined step sequences, such as cruciate (e.g., paw sequence: left forepaw, right forepaw, left hind paw, right hind paw and so on), alternate (e.g., right forepaw, right hind paw, left forepaw, left hind paw) and rotate (e.g., left forepaw, right forepaw, right hind paw, left hind paw). The regularity index illustrates the number of step sequences corresponding to the predefined locomotion patterns relative to the total number of paw placements, expressed in percentage.

## 2.8 | Von Frey hairs and allodynia

Von Frey hairs of different diameters (i.e., different forces) were used to assess secondary allodynia. Eighteen control and 23 SMR alert rats at P40 were placed in a Plexiglas chamber with a metal mesh floor, which allowed access to the plantar surface in the middle of the hind paws but avoiding the plantar pads and heel. After acclimation of the animal, von Frey hairs were applied smoothly perpendicular to the plantar surface over 1–2 sec until they bent. Rats were distracted with food to avoid vision of the monofilament application. A positive response was recorded when the rat withdrew the stimulated paw. Each monofilament was applied three times pseudo-randomly within a single session. The threshold value of allodynia for each rat was the lowest force applied with the monofilament at which 50% or more of the trials are positive.

## 2.9 | Open-field test

Spontaneous locomotor activity was assessed in an observation arena made of grey Plexiglas (100 cm diameter  $\times$  40 cm high) with a floor demarcated into 19 cm  $\times$  19 cm squares. Rats were first habituated to the arena covered with sawdust for 10 min. At the beginning of each session, each rat was placed into the centre of the field. Then, the number of squares visited (i.e., crossed lines), rearings and groomings were measured for 10 min, with the results divided into events occurring in

either the first or last 5 min. Twenty-six control and 28 SMR rats were tested only once in the open-field arena from P40 to P60.

## 2.10 | Actimetry

Spontaneous activity and locomotion were assessed in a home cage (27  $\times$  21.5  $\times$  41.5 cm with sawdust) equipped with a highly sensitive vibration platform (Activmeter, Bioseb) for 12 hours during the dark phase when rats were active. Connected to a computer the platform below the cage displayed on real-time activity (min), type of activity, position and motion of the animal, such as inactive immobility (e.g., sleep), active immobility including rearings detected by infrared beams and self-grooming/cleaning, slow (6–12  $\text{cm}\cdot\text{s}^{-1}$ ) and fast ( $>12 \text{ cm}\cdot\text{s}^{-1}$ ) moves, and the distance travelled (cm) during mobile activity.

## 2.11 | Object-recognition memory

Based on rat's spontaneous tendency to explore novelty, object recognition memory was assessed after different intervals of retention: 1 min, 4 hours, 1 day and 1 week. The exploration time of a new object was compared with the exploration time of a familiar object (Eichenbaum et al., 2007; Mumby et al., 2005). We used 40 control and 27 SMR rats that were tested from P40 to P60.

The apparatus consisted of an open-field arena (100 cm  $\times$  100 cm  $\times$  30 cm high) made of wood. A video camera was located above the field and connected to a video recorder and a monitor. Exploration times were determined offline using videotapes and a stopwatch. The two objects to be discriminated were plastic or metal toys without natural significance for the rats. All rats were given 2 habituation sessions of 10 min in the empty arena. On the training trial, the rat was placed between 2 different objects (A and B), facing the wall, and was allowed to explore the two objects for 5 min. The rat was then returned to its home cage. After a retention interval of 1 min, 4 hours, 1 day or 1 week, the experimenter removed both objects and replaced one with an identical copy of it (the "familiar" object, i.e. object A or B) while the other object was replaced with a "new" object (object C). The rat was then returned to the apparatus for a 3-min test trial. All combinations and locations of objects were used to reduce potential biases due to preference for particular objects or locations. Exploration of an object was defined as touching, palpating and sniffing the object with the paws, whiskers or nose. The time exploring each object during the training and the

test sessions was measured by a trained observer blind of the experimental groups. Object recognition performance was determined using a reaction to novelty, in which the mean duration of contacts with the “familiar” object was subtracted from the mean duration of contacts with the “new” object, and divided by the amount of time spent exploring the two objects (Delcour, Olivier, et al., 2012; Delcour, Russier, et al., 2012).

## 2.12 | Object-location memory

The apparatus was the same as in the object-recognition test and the age of animals ranged from P40 to P60 for 21 controls and 25 SMR rats. The same animals were used in the two memory tasks only for retention intervals of 1 min and 1 day. Rats were exposed to three different objects (D, E and F) in 3 training sessions (i.e. S1, S2 and S3) lasting 3 min each, with an inter-session interval of 1 min. The three objects were placed in a diagonal arrangement. After a retention interval of either 1 min, 4 hours, 24 hours or 1 week, the animal was allowed to explore the objects that had been replaced by identical copies (D, E and F), one of which was placed in its previous location in the arena while the other two objects were moved, so that the initial diagonal arrangement was switched to a triangular arrangement. Exploration time of objects was measured during the three training sessions and during the test session, of 3 min each. Object-location memory performance was determined using a ratio (reaction to spatial changes) in which the mean duration of contacts with the “not moved” object was subtracted from the mean duration of contacts (divided by two) with the 2 “moved” objects, and then divided by the amount of time spent exploring both “moved” objects (divided by two) and “not moved” object (Delcour, Olivier, et al., 2012; Delcour, Russier, et al., 2012).

## 2.13 | Tissue collection, histology and immunochemistry

To evaluate for the possible presence of brain lesions in the hippocampus, entorhinal, perirhinal and prefrontal cortices after SMR, we assessed brain sections after amyloid- $\beta$  precursor protein (APP) immunostaining and haematoxylin and eosin (H&E) staining. At the end of behavioral testing, 10 control rats and 10 SMR rats received terminal doses of anaesthesia (thiopentobarbital, 150 mg. Kg<sup>-1</sup> body weight, i.p.), before undergoing transcardial perfusion with 4% paraformaldehyde in phosphate buffer (0.10 M, pH 7.4). The brains were then

harvested, postfixed in the same fixative solution for 3 h, cryoprotected in sucrose 30% and frozen for cryosectioning. Sections to be immunostained for APP consisted of 15  $\mu$ m coronal sections (Delcour, Russier, et al., 2012). Alternate sections were stained with H&E. Sections were imaged using a Nikon E600, linked to a digital camera (Retiga EXI cooled camera, QImaging, Surrey, BC) and an image analysis system (Life Science, Bioquant Image Analysis Corp., Nashville, TN, USA). The heights of entorhinal cortices were measured in H&E stained sections using a 20x objective and the Auto-Width tool of the Bioquant Image Analysis program in which the inner and outer boundaries of structures were traced, and then mean layer thicknesses of the cortex were automatically generated.

## 2.14 | Data analysis

To apply parametric or non-parametric tests, the data normality, sphericity and homogeneity of the variances were first determined with Shapiro, Bartlett, Mauchly, F or var tests using R (R Core Team, 2021) in RStudio. Two-way and repeated-measures t and Welch tests, Wilcoxon rank test, one- and two-way and repeated-measures analyses of variance (mixed ANOVAs) along with Tukey multiple post hoc comparisons, and chi-square ( $\chi^2$ ) were performed with R or Statistica. The assumptions of the linear models used for statistics were checked and cross-validated by using residuals, the SD of residuals and adjusted R<sup>2</sup> or Akaike’s information criterion (AIC), as measures of the loss of predictive power and shrinkage in regression or a measure of the goodness-of-fit, respectively. In all parametric and non-parametric tests, we rather used adjusted or corrected p-values proposed in R software, depending on the test. Reaction to novelty or to spatial changes in object recognition memory was detected by comparing the time spent exploring the “familiar/not moved” versus the “new/moved” objects using paired t-tests within each group. Then, the magnitude of the reaction to either novelty or spatial changes was compared between the two groups using a two-sample t-test. Rats whose exploration time differed between the two types of objects during any of the familiarization sessions were discarded from the analyses. The investigators were blinded to rearing conditions throughout the different experimental sessions until statistical comparisons were performed. All procedures were videotaped and recorded times were double-checked by different experimenters. Data are expressed as means  $\pm$  S.E.M. Statistical significance was set at  $p < 0.05$ . All ANOVA and non-parametric analyses are reported in the Supplemental Results, except the post hoc tests mentioned in the text.

### 3 | RESULTS

#### 3.1 | Impact of SMR on body weight growth

Body weight was measured at birth (P0), P14 and P28 at the end of hind limb immobilization for SMR rats and P60, according to sex (Figure 1b). The body weight increased with age (age effect:  $p < 0.0001$ ), was lower in females than in males (sex effect:  $p < 0.0001$ ) and was decreased with SMR in comparison to controls (group effect:  $p < 0.0001$ ; see Supplemental Results). These effects were mainly reported at the end of the development at P60 (post hoc test:  $p < 0.002$ ; Figure 1b). At P60, the weight of females in control and SMR groups did not differ ( $p$ : n.s.), but control males tended to slightly weight more than SMR males ( $p < 0.06$ ; Figure 1b).

#### 3.2 | SMR impairs multisensory integration and sensorimotor performances in immature rats

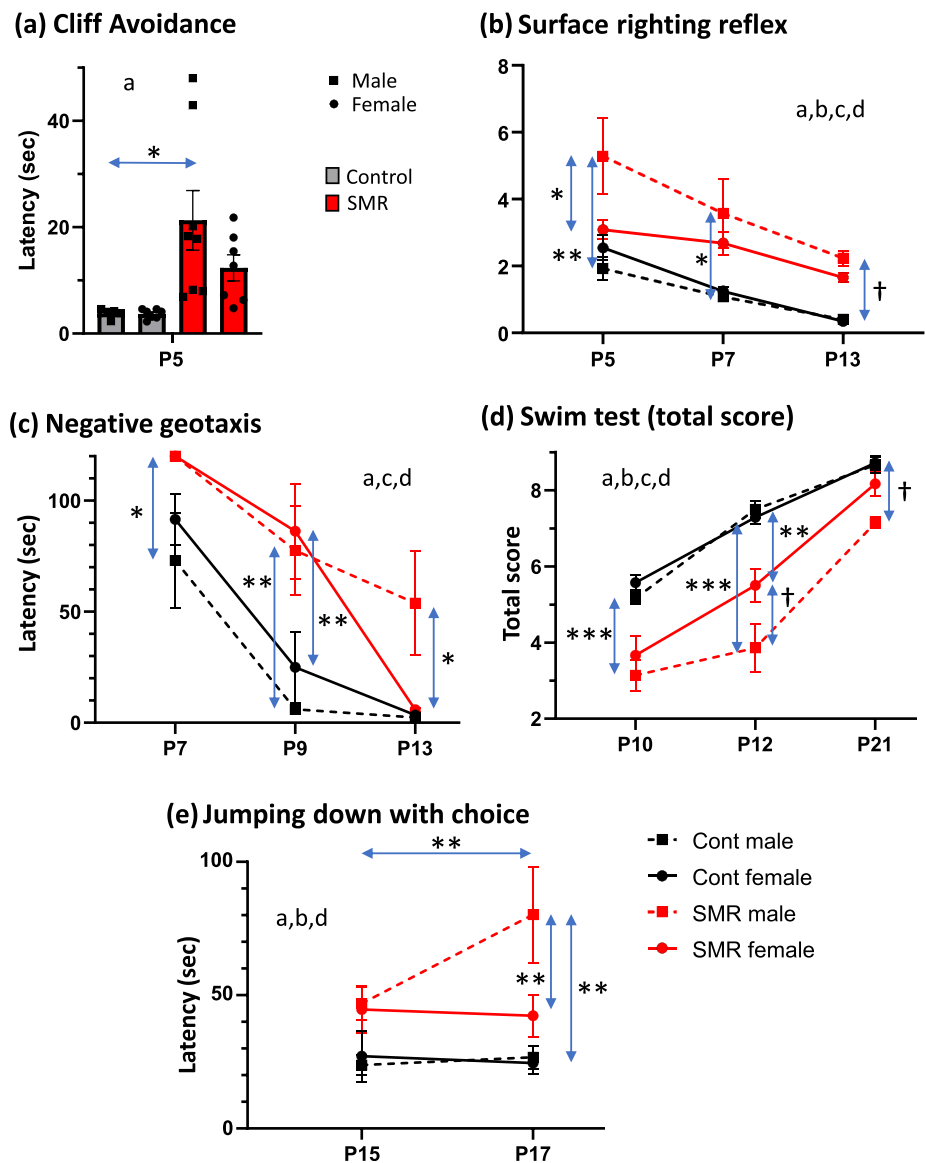
##### 3.2.1 | Impact of SMR on cliff avoidance

The latency to escape from the cliff was greater in SMR pups than in control pups (group effect:  $p < 0.02$ ; see Supplemental Results). SMR male pups showed a greater latency than control male pups (post hoc test:  $p < 0.02$ ; Figure 2a).

##### 3.2.2 | Effects of SMR on surface righting reflex

As expected, the latency to be back on the four paws decreased with age from P5 to P13 (age effect:  $p < 0.006$ ;

**FIGURE 2** Impact of a few days of movement restriction (SMR) on sensorimotor performance during development. (a) In the cliff avoidance, the latency to escape from the edge of a cliff at P5 was much larger in SMR pups than in controls. (b) During the righting surface reflex, the latency to regain all four paws from supine position was greater in SMR males at all ages considered, compared to sex-matched controls. SMR females only differed from SMR males at P5, but did not differ significantly from controls at any age. (c) In the negative geotaxis test, post hoc tests indicated that SMR males differed from control males at all ages considered, and from SMR females at P13. SMR females exhibit longer latencies than control females at P9 only. (d) In the swimming test, SMR males showed lower total scores at all ages considered, compared to controls and to SMR females at P12 only. The total score of the latter only differed from control females at P12 only. (e) The latency to jump in either empty cage or a cage with littermates was lower in SMR males at P17, compared to other groups at P17, and to SMR males at P15. a, significant effect of group; b, effect of sex; c, effect of age, d, significant interactions between factors; \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.0001$ ; †, tendency,  $0.08 < p < 0.1$ .





see Supplemental Results). SMR pups showed a longer latency than control pups (group effect:  $p < 0.002$ ; Figure 2b). Post hoc tests showed that SMR males exhibited longer latencies, compared to SMR females only at P5 ( $p < 0.02$ ) and to control males at P5 ( $p < 0.002$ ), P7 ( $p < 0.04$ ) and P13 ( $p < 0.08$ , tendency); whereas, control males and females did not differ (Figure 2b).

### 3.2.3 | Impact of SMR on negative geotaxis

SMR pups exhibited longer latencies to turn round on the inclined plan, compared to controls whatever the age (group effect:  $p < 0.0003$ ) and sex, but the latencies decreased with age (age effect:  $p < 0.0001$ ) whatever the group (age x group:  $p < 0.02$ ; age x sex:  $p < 0.04$ ; see Supplemental Results; Figure 2c). Post hoc tests indicated that SMR males exhibited longer latencies to turn, compared to control males at all ages ( $0.05 < p < 0.0002$ ) and to SMR females only at P13 ( $p < 0.05$ ); whereas, control males and females did not differ. SMR females showed longer latencies than control females only at P9 ( $p < 0.002$ ; Figure 2c). It is worth to note that all control pups exhibited a dorsiflexion of the tail when put head down whether of the age tested; whereas, the tail of SMR pups displayed a “corkscrew” shape from P3 up to P14.

### 3.2.4 | Influence of SMR on swimming development

Direction, angles of the head and use of limbs were considered in the swimming test and pooled together to obtain a total score, described here. Two-way ANOVA indicated significant effects in both groups (group:  $p < 0.0001$ ), showing lower total scores in SMR pups than in controls and sex (sex:  $p < 0.04$ ; see Supplemental Results; Figure 2d). We found a gradual increase in the total score over time from P10 to P21 (age:  $p < 0.0001$ ; group x age:  $p < 0.01$ ). Post hoc tests showed lower total scores in SMR males, compared to control males at P10 and P12 ( $p < 0.0001$ ) and a tendency at P21 ( $p < 0.1$ ; Figure 2d). SMR females exhibited lower total scores than control females only at P12 ( $p < 0.0002$ ); whereas, control males and females did not differ.

Concerning the scores for direction (sinking, floating, circling or relatively straight swim), head angles and limb use separately, two-way ANOVAs with repeated measures indicated comparable results, i.e., significant effects of group and age, but not of sex, nor interactions between factors (data not shown).

### 3.2.5 | Impact of SMR on jumping down with choice

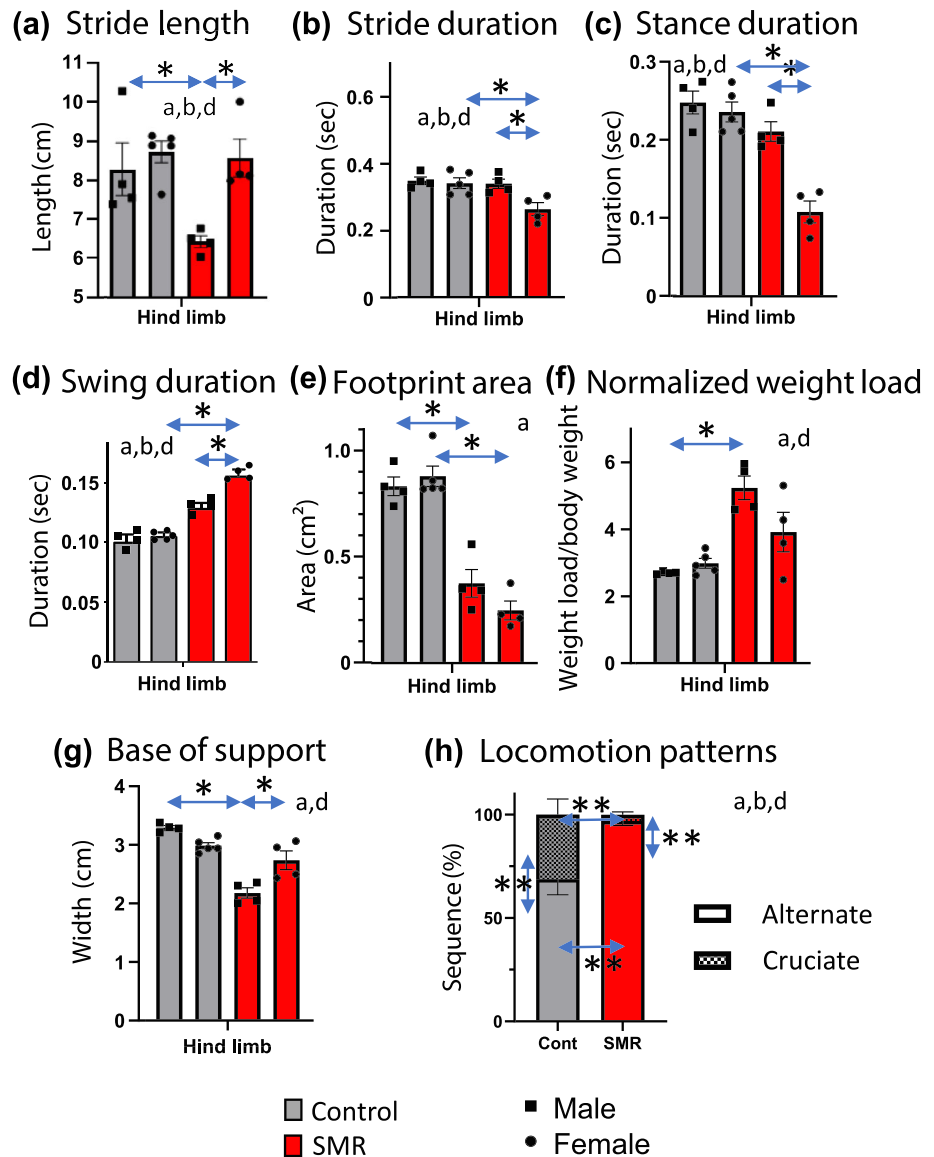
SMR rats displayed longer latencies to jump down into one of the cages containing either siblings or sawdust, compared to controls (group effect:  $p < 0.0003$ ); however, this effect differed according to the sex and age (group x sex x age:  $p < 0.03$ ; see Supplemental Results). Post hoc tests indicated that SMR males displayed longer latencies to jump compared to controls ( $p < 0.0002$ ) at P17 (Figure 2e).

### 3.2.6 | Deleterious effects of SMR on footprints, kinematics and movement patterns at P21

We used the catwalk system based on footprints of the hind limbs to assess the impact of SMR on the kinematics of locomotion at P21 in male and female rats. SMR male pups exhibited shorter strides length compared to control males (group effect:  $p < 0.04$ ; sex effect:  $p < 0.01$ ; post hoc tests:  $p < 0.03$  -SMR males versus male controls or SMR females; Supplemental Results; Figure 3a). Concerning the stride duration, we reported for the hind limbs a significant impact of SMR specifically in females (group x sex:  $p < 0.05$ ; post hoc tests:  $p < 0.03$  versus control females or SMR males; Figure 3b). Surprisingly, SMR males exhibited comparable stride durations as control males (Figure 3b). Similar results were obtained for the stance duration (group x sex,  $p < 0.005$  (Figure 3c), with SMR females displaying shorter stance durations for the hind limbs (post hoc tests  $p < 0.03$  versus SMR males or control females); whereas, SMR males did not differ from control males (Figure 3c). SMR animals displayed longer swing durations than controls (group effect:  $p < 0.0001$ ), this effect seemed greater in females exposed to SMR (post hoc test:  $p < 0.03$ ; Figure 3d).

Concerning the area of the footprints during locomotion on the walkway, two-way ANOVA indicated a significant group effect ( $p < 0.0001$ ) with a decreased footprint area in both SMR males and females (Figure 3e). For the weight load normalized to body weight, two-way ANOVA indicated an effect of group ( $p < 0.0002$ , Figure 3f), showing an increase during SMR and a significant interaction between group and sex ( $p < 0.03$ , Figure 3f). Post hoc tests indicated that the normalized weight load was only greater in SMR males, compared to control males ( $p < 0.03$ ; Figure 3f). There was a significant group x sex interaction for the base of support ( $p < 0.0004$ ), for which SMR males displayed the smallest base of support

**FIGURE 3** Effects of early sensorimotor restriction (SMR) on locomotor kinematics and patterns at postnatal day 21 (P21). Based on hind limb footprints, dynamic kinematics such as stride length (panel a), durations of the stride (panel b), stance (panel c) and swing (panel d) were analyzed after SMR (see supplemental results). SMR males exhibited the lowest length of stride (a), but SMR females displayed the lowest durations of stride and stance, and the largest duration of swing for the hind limbs. (e) The footprint area of the hind paws was smaller in SMR males and females, compared to control counterparts, indicative of toe-walking or digitigrade locomotion. (f) In contrast, the weight load relative to individual body weight was greater in SMR males, compared to control males. (g) The base of support was the smallest in the hind limbs of SMR males. (h) Locomotion patterns correspond to the order in which paws were placed on the walkway of the catwalk system with predefined sequences. Control rats at P21 exhibited mainly two patterns (i.e. alternate and cruciate with a higher proportion of the former); whereas, SMR rats display almost exclusively the pattern alternate. Yet, the pattern rotate was almost absent in the two groups and does not appear in the plots. Same conventions as Figure 2.



(post hoc test:  $p < 0.03$ ; Figure 3g). It is worth to note a comparable deleterious impact of SMR on the fore-limb kinematics for the stride length, stride duration, normalized weight load and base of support (data not shown).

Analysis of locomotion patterns (i.e., alternate, cruciate and rotate) based on the footprints of the hind limbs revealed that SMR significantly altered the sequence patterns of locomotion (group  $\times$  patterns interaction:  $p < 0.0004$ ) whether of the sex. Concerning the patterns, the pattern “rotate” was almost absent, the pattern “cruciate” was present but much less than the pattern “alternate” whatever the group considered (effect of patterns:  $p < 0.0001$ ; Figure 3h). Concerning the repartition of the patterns per group, “alternate” was much greater in

SMR rats ( $96.88 \pm 2.20\%$ ) than in controls ( $68.68 \pm 7.50\%$ ; group effect:  $p < 0.007$ ) while “cruciate” was less present in SMR rats ( $3.0 \pm 1.36\%$ ) compared to controls ( $31.30 \pm 7.50\%$ ; group effect:  $p < 0.005$ ; Figure 3h), indicative of a stereotyped pattern of locomotion after SMR.

To sum up, the kinematics of locomotion at P21 were affected by developmental SMR, with a stronger impact in males. The footprint area was drastically reduced in SMR rats, indicative of digitigrade locomotion. In addition, the relative weight load was increased while the base of support was reduced in SMR males. Finally, SMR animals exhibited a stereotyped pattern of locomotion limited to the “alternate” sequence at P21.

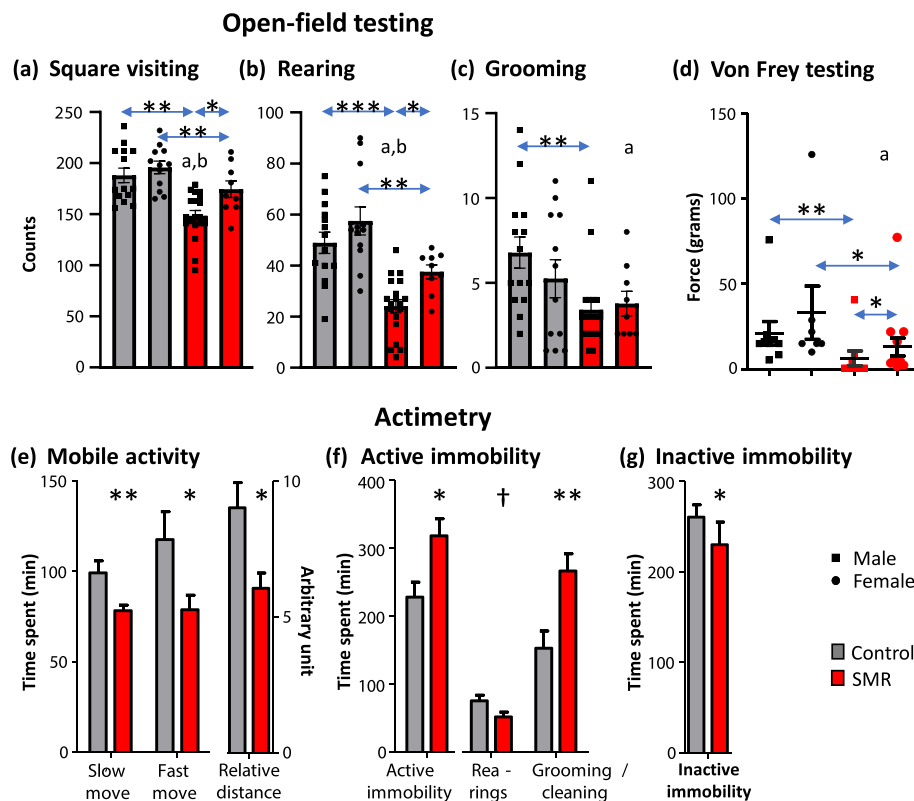
### 3.3 | SMR had enduring deleterious effects on general activity, pain threshold and object memory

#### 3.3.1 | Spontaneous locomotor exploration in open-field

SMR induced reduced spontaneous activity in the open-field with less squares visited (group effect:  $p < 0.0001$ ; see Supplemental Results), especially in SMR males which exhibited the least exploration (sex:  $p < 0.02$ ; post hoc tests:  $0.01 < p < 0.0002$ ; Figure 4a). In the same line, SMR rats did less rearings, compared to controls (group effect:  $p < 0.0001$ ) and SMR males did the least rearings (sex:  $p < 0.009$ ; post hoc tests:  $0.007 < p < 0.0002$ ), compared to other subgroups (Figure 4b). In addition, self-grooming activity was reduced in SMR rats, compared to controls (group:  $p < 0.003$ ; Figure 4c) and only SMR males differed significantly from male controls (post hoc test:  $p < 0.03$ ).

#### 3.3.2 | Actimetry

We used 8 control and 8 SMR rats at P40 with unequal repartition of the two sexes to compare them adequately. Compared to the control condition, SMR reduced the time spent in mobile activity, including slow (Wilcoxon test,  $p < 0.01$ ; see Supplemental Results) and fast move ( $p < 0.03$ ) during the night period and the relative distance (i.e., distance normalized by the total activity time for each rat) travelled by SMR rats was smaller ( $p < 0.04$ ; Figure 4e). As expected, the active immobility time was greater after SMR ( $p < 0.02$ ), in which the time spent for grooming and cleaning was greater in SMR rats ( $p < 0.007$ ), compared to controls, while that for rearings tended to be smaller in SMR rats ( $p < 0.06$ ; Figure 4f). Surprisingly, the time spent during inactive immobility, such as sleep mainly, was reduced after SMR (Wilcoxon test,  $p < 0.02$ ; Figure 4g). Thus, SMR rats moved less, spent



**FIGURE 4** Influence of early movement restriction (SMR) on pain and behavior into adulthood. (a–c) Performance in the open-field test in adult rats. The numbers of squares crossed (panel A) and rearings (panel B), and grooming activity (panel EC) were lower in SMR rats than in controls, with the lowest performance in SMR males. (d) The force applied using a Von Frey hairs to elicit a hind paw withdrawal was smaller in SMR rats than in controls, showing reduced sensitivity to pain or allodynia. (e–g) Assessment of spontaneous activity in home cage during the night, active period of adult rats that experienced early sensorimotor restriction (SMR), including mobile activity (e), active immobility (f) and inactive immobility (g). (e) Slow and fast moves during mobility were reduced in SMR rats, as well as the relative distance travelled, compared to controls. (f) In line, the active immobility increased after SMR, especially the time spent for self-cleaning and self-grooming while that for rearings tended to decrease. (g) Interestingly, the spent in inactive immobility, such as sleep, decreased in SMR rats, compared to controls. Same conventions as Figure 2; †, tendency,  $p < 0.06$ .

more time doing self-cleaning and -grooming and slept less, compared to controls during the night phase.

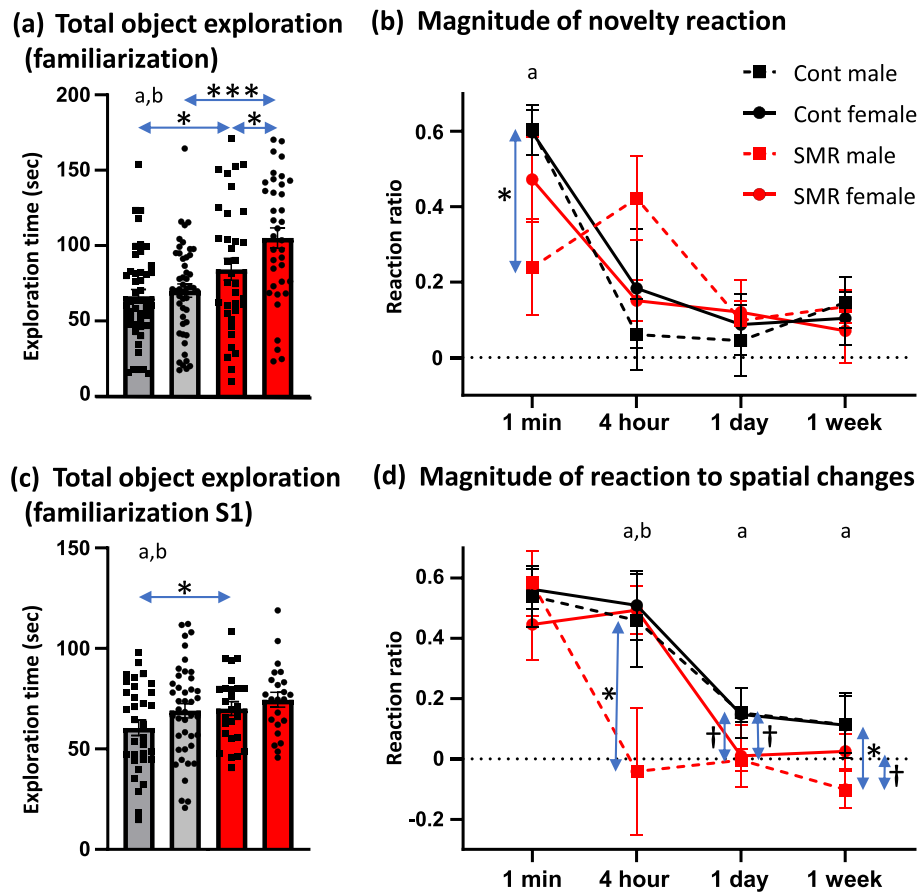
### 3.3.3 | Von Frey hairs and allodynia

SMR decreased the force to induce a withdrawal of the hind paws, compared to control condition (group effect:  $p < 0.04$ ; see Supplemental Results; Figure 4d). Post hoc tests indicated that SMR males exhibited the lowest force for withdrawal ( $p: 0.007 < p < 0.02$ ; Figure 4d). Thus, SMR appeared to increase pain sensation (i.e., allodynia) to Von Frey hairs when applied to plantar pads. SMR males showed the greatest signs of allodynia, relative to other subgroups.

### 3.3.4 | Non-spatial object recognition memory tasks

When we pooled together the exploration time of the two objects during the familiarization session of the four retention intervals, SMR rats exhibited a greater exploration of objects (group effect:  $p < 0.0001$ ; sex:  $p < 0.05$ ; see Supplemental Results), in which SMR females explored the most (post hoc tests:  $0.0001 < p < 0.04$ ), compared to other animals (Figure 5a).

For the object-recognition task, the different retention intervals ranged from 1 min (short-term memory), 4 hours (consolidation time) to 1 day and 1 week for long-term memory. During testing, all rats reacted to novelty (data not shown). For the magnitude of novelty



**FIGURE 5** Influence of postnatal sensorimotor restriction (SMR) on performance in object-recognition (non-spatial; a,b) and object-location (spatial; c,d) memory tasks. (a) The time spent exploring the two objects was greater in SMR rats, especially in SMR females, compared to controls during the 5-min familiarization session when all retention intervals were pooled together. (b) The magnitude of reaction to novelty was lower only in SMR males after a short (1 min) delay of retention but not in the other retention intervals, indicative of deficits in either short-term memory, integration of object features or attention. (c) When all retention intervals were pooled together, the time spent exploring the three objects during the first session (S1) of familiarization was larger in SMR males than in control males, showing object exploratory hyperactivity. Note that SMR females spent the longest time exploring the objects in (a) and (c). (d) SMR males displayed smaller reactions to spatial changes, compared to control males at 4 hours, 1 day ( $p < 0.08$ ) and 1 week, and to SMR females at 1 week ( $p < 0.08$ ). Compared to control females, SMR females tended to exhibit smaller reactions to spatial changes only at 1-day interval ( $p < 0.06$ ). Same conventions as Figure 2. †, tendency,  $0.06 < p < 0.08$ .

reaction at the retention interval of 1 min, SMR males reacted the least (group effect:  $p < 0.008$ ; post hoc tests:  $p < 0.05$ ), compared to other animals (Figure 5b). Conversely, we found no significant impact of SMR in the other retention intervals (Figure 5b).

### 3.3.5 | Spatial object recognition memory tasks

To validate the object-location task, we found that the time spent exploring the 3 objects (i.e. two “moved” objects and one “not moved” object) gradually decreased over the three familiarization sessions (S1 to S3; session effect:  $p < 0.0001$ ; see Supplemental Results) whether of the retention interval, but did not differ between the groups (group effect:  $p$ : n.s.; data not shown). The exploration time of each object was comparable during each familiarization session and between the two groups and sexes (data not shown).

When we pooled together the exploration time of all objects during the first familiarization session (i.e. S1), SMR rats explored the objects more (group effect:  $p < 0.05$ ), compared to controls (Figure 5c). SMR males explored the objects more than the control males (post hoc tests:  $p < 0.05$ ). It is worth to note that SMR females appeared to explore the most the objects ( $p$ : n.s.; Figure 5c).

Concerning the magnitude of reaction to spatial changes, we found no significant impact of SMR at the retention interval of 1 min, but SMR rats reacted less at 4 hours (group effect:  $p < 0.08$ , tendency), 1 day (group:  $p < 0.02$ ) and 1 week (group:  $p < 0.05$ ), compared to controls. Compared to control males, SMR males reacted less at 4 hours (post hoc test:  $p < 0.05$ ), 1 day (post hoc test  $p < 0.08$ , tendency) and 1 week (post hoc test  $p < 0.05$ , Figure 5d).

## 3.4 | Histopathology in the hippocampal complex and prefrontal cortex after SMR

Increased APP immunostaining, a sign of axonal degeneration (Delcour, Olivier, et al., 2012; Hellewell et al., 2010), was observed in the hippocampus dentate gyrus and disruption of the CA3 region of the hippocampus in SMR rats, relative to control rats ( $7.67 \pm 1.66$  versus  $1.21 \pm 0.52$ , respectively,  $p < 0.05$ ) (Figure 6a–i). Specifically, an increase in APP immunostaining was observed in neurons and processes in the dentate gyrus of SMR rats, relative to control rats (Figure 6c, f–h versus A). However, the SMR rats showed no clear disorganization or thinning of neurons in the dentate gyrus

(Figure 6e versus B). The CA3 region was disorganized in the SMR rats, relative to control rats (Figure 6e versus C) and showed a small increase in APP immunostaining in the SMR rats, relative to control rats ( $3.64 \pm 0.23$  versus  $0.63 \pm 0.21$ , respectively,  $p < 0.05$ ) (Figure 6i). A moderate increase of APP immunostaining was observed in the perirhinal cortex of SMR rats relative to control rats, although no clear laminar disruption was observed ( $5.46 \pm 0.32$  versus  $0.68 \pm 0.14$ , respectively;  $p < 0.05$ ) (Figure 7a–d). A low increase of APP immunostaining was observed in the entorhinal cortex of SMR rats relative to control rats ( $2.34 \pm 0.61$  versus  $0.51 \pm 0.20$ , respectively;  $p < 0.07$ , tendency); again, no clear laminar disruption was observed (Figure 7e–h). In contrast, no APP immunostaining differences were observed in the prefrontal cortex of SMR versus control rats (Supplemental Figure S1A,B).

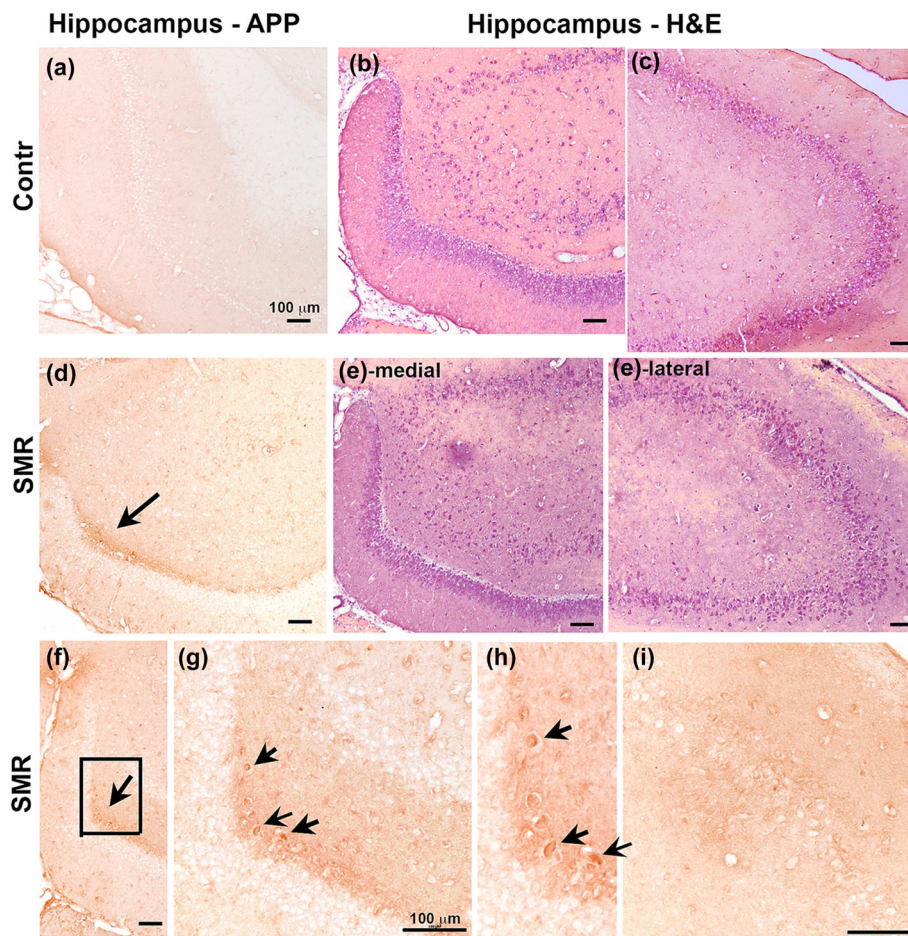
## 4 | DISCUSSION

In prior studies, developmental SMR led in adult rats to degraded postural and locomotor abilities, musculoskeletal histopathology, hyperexcitability within the sensorimotor circuitry and maladaptive cortical plasticity leading to functional disorganization of the primary somatosensory and motor cortices (Coq et al., 2008; Delcour, Massicotte, et al., 2018; Delcour, Russier, et al., 2018; Strata et al., 2004). The present study is the first one to our knowledge to evaluate the deleterious impact of SMR on the integration of multisensory information for the development of sensorimotor reflexes and locomotor skills and on non-motor functions, such as making choices based on familiarity, general activity levels, pain and object-memory abilities during development and adulthood.

### 4.1 | Early emergence of neurodevelopmental disorders

Briefly, gait and posture mature gradually from P2 with crawling and head pivoting to P15–16 (Altman & Sudarshan, 1975; Gramsbergen, 2001) or P21 (Clarac et al., 1998) with adult patterns. The cerebellum appears involved early in many sensory, motor and non-motor functions such as multisensory integration, sensorimotor learning, emotion, cognition and autonomic control in rats and humans (Caligiore et al., 2017; Schmahmann, 2019). We investigated the impact of SMR on the early emergence of sensorimotor reflexes, using cliff avoidance, surface righting and negative geotaxis tests that involve multisensory and motor integration during development.



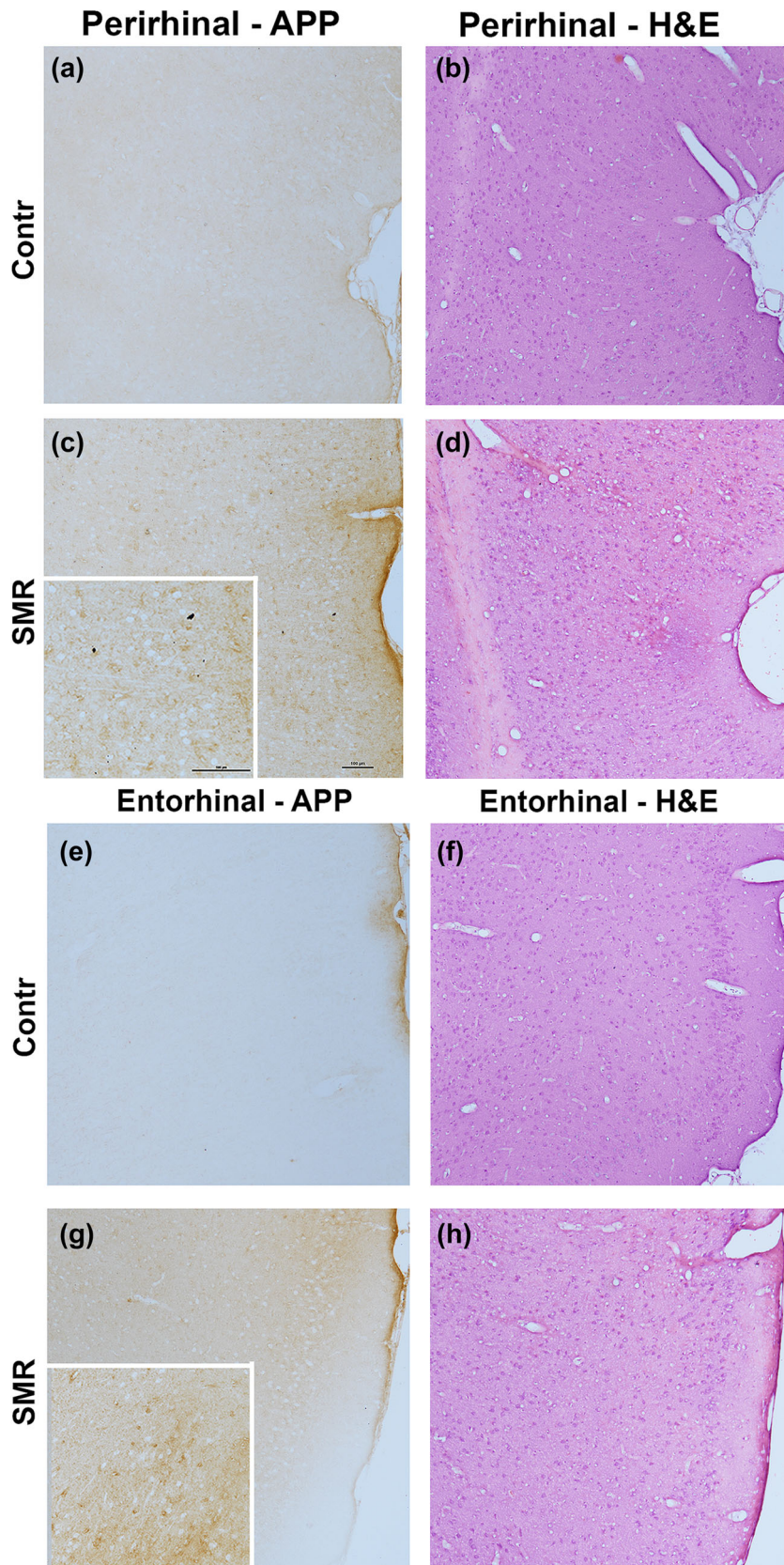


**FIGURE 6** Amyloid- $\beta$  precursor protein (APP) immunostaining and haematoxylin and eosin (H&E) staining of the hippocampus of SMR and control rats. (a–c) Representative control rat images, showing no APP staining in the dentate gyrus of a Control rat (panel a), and normal organization of the dentate gyrus and CA3 regions of a Control rat after H&E staining (panels b and c). A photomontage is utilized in panel C to show the entire CA3 region. (d) A representative image of increased APP staining in the dentate gyrus of an SMR rat (arrow). (e) A photomontage of images from an H&E stained hippocampus of an SMR rat. The right side of this photomontage contains the CA3 region and shows clear laminar disruption. (f–h) An image of an APP immunostained dentate gyrus of a different SMR rat than shown in panels d and e. Panel G is an enlargement of the region indicated by the box in panel f, while panel h is an enlargement of the APP+ neurons indicated by arrows in each panel. (I) An image a CA3 region of an SMR rat showing moderate levels of APP immunostaining in scattered cells and processes. Scale bars = 100  $\mu$ m in each panel.

SMR pups exhibited a delayed emergence of such reflexes already after a few days of SMR and deficits in the integration of multisensory information to perform these tasks. In the absence of vision at P5, cliff detection seems related to touch through forepaw and whisker scanning (Altman & Sudarshan, 1975). Righting reflex and negative geotaxis testing seem to involve touch, proprioception and vestibular activation to detect backward or head-down positions. These tests also involve inter-limb motor coordination (Altman & Sudarshan, 1975). However, proprioception seems to become functional in typical conditions from P12 as muscle spindles and fusiform innervation become operative (Milburn, 1973), so that integration of multisensory information appears altered in early stages by SMR, especially in males.

Right after birth, postural control is not effective; yet, the early locomotor activity can be studied using swimming while pups move in microgravity. Like controls, the scores of SMR pups for swimming increased from P10 to P21 but stayed lower than those of controls at all ages considered, especially in SMR males. We then tested locomotor activity at P21 based on hind limb footprint recordings. Compared to controls, the stride length of hind limbs was shorter only in SMR males. The stride and stance durations were shorter in SMR rats while the swing duration was longer, especially in SMR females. At P21, the hind limb footprint area was smaller during SMR while the normalized weight load was increased during SMR, mainly in SMR males. This smaller footprint, concomitant to an overextension of the knee and





**FIGURE 7** Amyloid- $\beta$  precursor protein (APP) immunostaining and haematoxylin and eosin (H&E) staining of entorhinal and perirhinal cortices of SMR and control rats. (a,b) Representative control rat perirhinal cortex images. (c,d) Representative SMR rat perirhinal cortex images. The perirhinal cortex shows a moderate level of immunostaining of neuropil in the perirhinal cortex. This inset in C shows a higher-power representative image from an SMR rat. (e,f) Representative control rat entorhinal cortex images. (g,h) Representative SMR rat entorhinal cortex images. The entorhinal cortex shows only low level of immunostaining of neuropil in the entorhinal cortex. This inset in C shows a higher-power representative image from an SMR rat. Scale bar in panel C = 100  $\mu$ m and applies to all but the inset panels. Scale bar in the inset image in panel C = 100  $\mu$ m, and applies to the inset in panel G.

ankle corresponds to early digitigrade locomotion that we previously described in adult SMR rats (Delcour, Massicotte, et al., 2018; Strata et al., 2004). This

digitigrade locomotion resembles toe-walking or pes equinus, the most common symptom observed in spastic diplegic children and adults with cerebral palsy (Rodda

et al., 2004). Toe walking can also be encountered in children with ASD who often stand and run on their tiptoes (Valagussa et al., 2018), but has not been reported so far in children with DCD. For the locomotion patterns at P21, SMR pups displayed almost exclusively the alternate sequence (97%), indicative of a stereotyped pattern of locomotion during SMR. The over-representation of the alternate sequence persisted in adult SMR rats (Canu et al., 2022), confirming the stereotyped pattern of locomotion during and after SMR. Thus, degraded sensorimotor abilities and multisensory integration may reflect the disrupted organization of the sensorimotor networks, including the cerebellum, and atypical motor learning (Clarac et al., 1998; Gramsbergen, 2001; Smits-Engelsman & Wilson, 2013; Wilson et al., 2017). The delays in the emergence of sensorimotor abilities appeared not completely caught up by SMR males over time, as observed in DCD (Smits-Engelsman & Wilson, 2013; Wilson et al., 2017). Several studies have reported sensory deficits, altered somatosensation and body internal representation and pain as well in children with DCD or ASD (Brown et al., 2020; Kempert et al., 2019). However, we cannot completely rule out the possible impact of reduced mobility and increased fatigability on the performance in SMR animals, although we minimized such an impact by maximizing the time delay between trials for each animal. Stress even minimized by handling may have also an impact on our behavior results. Further studies are needed to determine the possible impact of these factors.

To examine higher functions, such as familiarity and decision-making, we used the jumping down with choice task. At P17, only SMR males exhibited longer latencies to jump, suggesting possible alterations of familiarity and decision-making in the early stages (Altman & Sudarshan, 1975; Khalki et al., 2012).

## 4.2 | SMR leads to enduring changes in pain, general activity and object memory

By applying different forces with Von Frey hairs, we found that SMR increased pain sensitivity, especially in males. In fact, the hyperexcitability previously observed in the lumbar spinal cord at P30 (Canu et al., 2022) and P60 (Delcour, Massicotte, et al., 2018) and altered neuronal response properties in the primary somatosensory cortex (Delcour, Russier, et al., 2018) may explain allodynia in SMR rats. These results tend to show increased allodynia, resulting in hyperalgesia after SMR.

During the active, night period in the actimetry cage, movements, rearings and sleep were reduced while immobile activity such as grooming/cleaning increased.

In contrast, the spontaneous locomotor activity in free-access activity wheels of SMR rats a month after the cessation of the SMR casting was much higher and sustained (Canu et al., 2022). Thus, the spontaneous locomotor activity or general activity levels of SMR rats does not appear to depend on motor skills but to rely on rats' internal state, stress, anxiety and emotionality (Kalueff et al., 2016; Sturman et al., 2018), which seems different in SMR rats, compared to controls. Animal models of ASD based on either on prenatal administration of valproic acid (VPA) or prenatal immune activation displayed decreased rearing (Al Sagheer et al., 2018; Haida et al., 2019). Self-grooming is generally considered in rodents to reflect repetitive and stereotyped behaviors, as observed in children with ASD (Kalueff et al., 2016). Surprisingly, SMR rats did less grooming than controls in the open-field arena during the day phase, and less active for 10 min; whereas, SMR rats spent much more time for self-grooming and cleaning in the actimetry cage during the night, active period for 12 hours, which could be more representative of the genuine behavior of SMR animals. Interestingly, animal models of ASD based on early neuroinflammation also showed increased time spent on grooming, indicative of increased stereotypies (Al Sagheer et al., 2018; Haida et al., 2019; Kalueff et al., 2016).

Our SMR rats exhibited exploratory hyperactivity during the first session of the object memory tasks, but not in the open-field. Animal models of ASD exhibited decreased exploration in the open-field (Haida et al., 2019). It seems that hyperactivity depends on hippocampal disorganization and/or excitation/inhibition imbalance in the prefrontal cortex (Del Arco et al., 2011; Rahi & Kumar, 2021). SMR rats exhibited axonal degeneration in the dentate gyrus, CA3 with laminar disruption and entorhinal cortex, but not in the prefrontal cortex. Thus, we found no marked disorganization within the hippocampal and prefrontal areas to explain such a hyper-exploration of objects. We think that SMR required more exploration time than controls to extract the pertinent information from the objects and environment for familiarization, as found after prenatal hypoxia-ischemia (Delcour, Olivier, et al., 2012; Delcour, Russier, et al., 2012; Ohshima et al., 2016).

Since impairments in visual-spatial functions and memory have been observed in children and adults born very preterm or with DCD, including ASD or ADHD (Biotteau et al., 2020; Paquet et al., 2019; Rose et al., 2011), we explored the impact of SMR on object recognition memory. SMR rats appeared to display novel object recognition memory impairments for the short retention interval of 1 min. Surprisingly, SMR rats showed intact performances for the 4-hour delay. Short-



term memory deficits in object recognition may result from disturbances in encoding object features as SMR exhibited hyperactivity in the first exploration of objects. According to the literature (e.g., Eichenbaum et al., 2007; Warburton, 2018), such a deficit in novel object recognition likely results from damage/disconnections within the ventral stream preferentially involved in information processing to extract object features and memory. We found axonal degeneration and laminar disorganization in the hippocampus, and moderate axonal degeneration in the perirhinal and entorhinal cortices. Lesional studies reported the involvement of the lateral entorhinal and perirhinal cortices and hippocampus in the novel object-recognition task (Delcour, Russier, et al., 2012; Eacott & Norman, 2004; Eichenbaum et al., 2007; Marks et al., 2018; Parron et al., 2004), which seemed altered after SMR. Alternatively, we cannot rule out the possible influence of exploratory hyperactivity and/or attention disorders in the short-term deficits in object-recognition tasks (Bardgett et al., 2011; Pires et al., 2009).

SMR rats also appeared to display deficits in object-location memory only for the longer retention intervals (4 hours, 1 day and 1 week), but not after 1 min of retention, suggesting possible deficits in consolidation and long-term memory in the object-location task. The re-exploration of « moved » and « not moved » object between the last familiarization session and the test session indicates that both groups of rats needed to re-encode the long-term spatial configuration of objects. These results may confirm impairments after SMR in processing and encoding spatial information. Since consolidation involves the transfer of information from the hippocampus to cortical structures (Winocur et al., 2010), the long-term memory deficits found after SMR seem eventually related to altered parahippocampal structures, including the entorhinal, perirhinal and postrhinal cortices (Delcour, Russier, et al., 2012).

### 4.3 | SMR has a sex-dependent impact on behavior

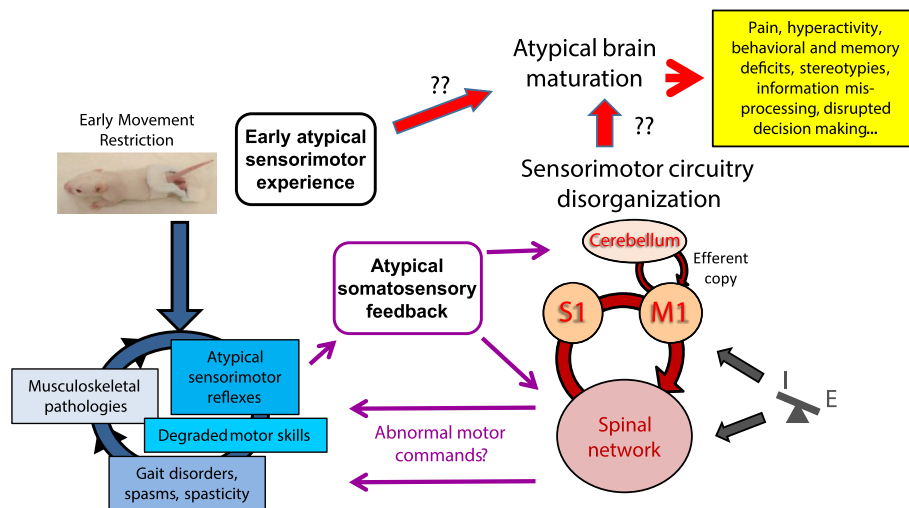
DCD appears 2 to 7 times more common in males compared to females (Rinat et al., 2020), as in ASD (ratio 3:1) (Al Sagheer et al., 2018) and ADHD (ratio 2:1) (Rouleau & Reduron, 2020). Interestingly, we found a differential impact of SMR between males and females throughout the different behavioral testings used here. Briefly, SMR male pups developed even poorer performance or delayed abilities than SMR females on the early sensorimotor and decision-making tests. Performance of SMR males appeared even more degraded than that

of females during gait and posture at P21. SMR females tended to exhibit better performance in most of the behavioral tests and greater exploratory activity, compared to SMR males.

Several studies reported sex-dependent vulnerability to neurodevelopmental disorders in both human and animal models, showing that young males were more affected than young females by perinatal adverse events, and more prone to develop brain damage and detrimental outcomes, the so-called “female advantage” (Dieu-Lugon et al., 2020). In fact, estrogen versus androgen receptors appear crucial for the expression of sexually dimorphic neuroanatomy, behaviors or protection against brain injury. For instance, male pups display more NeuN+ and GFAP+ cells in the hippocampus than females via the activation of androgen receptors (Zhang et al., 2008). The hippocampus of females appears more protected than males to GABA- and glutamate-induced excitotoxicity, in relation to sex-dependent microglial activation (Dieu-Lugon et al., 2020). Microglia and inflammatory processes appear also involved in brain development and brain-lesion resistance, and are highly dependent on sex (Mirza et al., 2015; Turano et al., 2019). In the immune models of ASD, males show higher motor impairments and social deficits, compared to females that only exhibit motor deficits (Al Sagheer et al., 2018; Haida et al., 2019). Like in SMR males, VPA-exposed males displayed reduced rearings, increased immobility and reduced locomotor activity, compared to VPA-treated females (Al Sagheer et al., 2018). Further studies are needed to investigate the possible role of early inflammation in SMR.

### 4.4 | Functional implications

We previously demonstrated that early SMR throughout limited amounts and abnormal patterns of movements and atypical somatosensory feedback induced peripheral disturbances, such as musculoskeletal histopathology, muscular atrophy and dysfunction, locomotor impairments including toe-walking and the presence of spasms and spasticity, that were reported in adulthood through a self-perpetuating cycle (Figure 8, *left part*; Canu et al., 2022; Coq et al., 2020; Delcour, Russier, et al., 2018). In the present study, we found that several sensorimotor impairments occurred in the early stages of development. We postulate that these early sensorimotor impairments produce in turn atypical somatosensory feedback to the immature sensorimotor circuitry, including the lumbar spinal network, and the primary somatosensory and motor cortices (Canu et al., 2022; Delcour, Russier, et al., 2018). From our present findings, we also think



**FIGURE 8** Schematic illustration of the deleterious impact of developmental SMR on the interplay between the periphery, sensorimotor circuitry and brain development. Early movement restriction provides early atypical sensorimotor experience, which leads to musculoskeletal pathologies including muscle atrophy, hyperreflexia, signs of spasms and spasticity, and gait disorders including toe-walking. In turn, gait disorders and muscle dysfunctions provide atypical somatosensory feedback or reafference to the immature sensorimotor circuitry; mainly the spinal cord network, the primary somatosensory (S1) and motor (M1) cortices and the cerebellum, which operates as an estimator, predictor and comparator of movements through the efferent copies and reafference towards the M1 cortex for further movement adaptation. We suppose that such an atypical reafference and abnormal operations of the cerebellum lead to a gradual and enduring, functional disorganization of the somatosensory and motor maps and spinal network, including imbalance between excitation (E) and inhibition (I) towards hyperexcitability, through maladaptive plasticity, and thus producing abnormal motor commands which finally aggravate gait disorders, spasms, spasticity and musculoskeletal abnormalities into interrelated self-perpetuating loops. Based on internal models and embodiment frameworks, we wonder whether the early functional disorganization of the sensorimotor circuitry including the cerebellum, also involved in non-motor functions, drives the atypical development and refinement of the brain, including associative areas, hippocampal and prefrontal networks, thus leading to the hyperactivity, memory deficits, impairments in the processing and integration of sensory information, as observed in the present study. One can also consider an alternative point of view, in which the sensorimotor deficits related to SMR would limit and disrupt the typical social and environmental interactions leading directly to atypical brain maturation and function.

that the cerebellum may be also involved in this disorganization of the sensorimotor circuitry (Dooley et al., 2021; Glanz et al., 2023; Gramsbergen, 2001). In the absence of obvious brain damage, we also postulate that the early atypical somatosensory reafference likely drives abnormal patterns of brain activity and an aberrant integration of multisensory information, leading to a functional disorganization of the sensorimotor maps. This functional disorganization appears to be maintained or even aggravated into adulthood throughout maladaptive but physiological mechanisms of plasticity and self-perpetuating loops (Figure 8, right part; Canu et al., 2019; Coq et al., 2020; Delcour, Russier, et al., 2018).

It is now well admitted that the development of body representation, movement repertoires, multisensory integration and motor control are under the regulation of electrical brain activity and oscillations through early spontaneous movements, sensorimotor experience and reafference in rodents (Cossart & Khazipov, 2022; Glanz et al., 2023; Luhmann & Khazipov, 2017), as well as in children (Blumberg & Adolph, 2023; Geertsen et al., 2017; Molnár et al., 2020). The functional disorganization of the

sensorimotor circuitry is likely to produce atypical motor commands, through maladapted choices within the motor repertoires (Glanz et al., 2021; Hadders-Algra, 2018), thus leading to impaired sensorimotor skills, locomotion and motor learning, as observed in patients with DCD (Biotteau et al., 2020; Gill et al., 2020; Vaivre-Douret et al., 2016). We postulate the existence of three interplaying, self-perpetuating cycles (see Figure 8): the first is related to peripheral changes, including degraded gait and motor skills, increased stretch reflex and musculoskeletal pathologies; the second involves the sensorimotor circuitry. The third self-perpetuating cycle corresponds to the interplay between the peripheral loop and the sensorimotor circuitry that are interconnected by the atypical reafference and atypical motor commands that likely drive abnormal movements.

In addition to sensorimotor disturbances, we showed here that developmental SMR led to atypical general activity levels, hyperactivity, stereotypies and deficits in choices based on social familiarity and in object memory abilities. Yet unresolved, as depicted in Figure 8, we question whether the atypical development of sensorimotor



circuitry and/or atypical social and environmental interactions related to motor impairments are at the origin of deficits in information processing and integration, general activity levels and non-motor abilities within an embodied framework (Blumberg & Adolph, 2023; Molnár et al., 2020; Petrosini et al., 2022). In addition, we found reduced sleep activity during SMR that may also contribute to the disorganization of the sensorimotor and brain circuitries, as recently proposed (Blumberg et al., 2022; Dooley et al., 2021).

Taken together, our rat model of SMR appears to recapitulate the main motor and non-motor symptoms observed in children with DCD, ASD and ADHD and we have proposed here some mechanisms that may trigger the emergence of these neurodevelopmental disorders. Our animal model based on functional sensorimotor misdevelopment seems promising to understand further the early mechanisms of the emergence of disorders and to test new leads for prevention or early remediation of these neurodevelopmental disorders.

#### AUTHORS CONTRIBUTIONS

Conceptualization, H.K., C.K., M.D., M.H.C., J.O.C.; Methodology, H.K., M.D., M. A., M.F.B., J.M.B., E.D., M.H.C., J.O.C.; Investigation H.K., D.L., C.K., M.D., M.A., O.D., M.K., E.D., M.H.C., M.F.B., J.O.C; Project Administration, J.O.C.; Resources, M.H.C, J.M.B., M.F.B., J.O.C.; Formal Analyses, H.K., D.L., M.D., M.H.C., M.F. B, J.O.C.; Writing and Editing, H.K., M.D., J.M.B., M.H.C., M.F.B, J.O.C.; Supervision, J.O.C.

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#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

#### PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16594>.

#### DATA AVAILABILITY STATEMENT

Behavioral data supporting the findings of the present study are available at: <https://entrepot.recherche.data.gouv.fr/dataset.xhtml?persistentId=doi:10.57745/8AH0DN>.

Brain sections used in this study are no longer available for further histology, but histological data are available upon reasonable request.

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#### REFERENCES

- Al Sagheer, T., Haida, O., Balbous, A., Francheteau, M., Matas, E., Fernagut, P.-O., & Jaber, M. (2018). Motor impairments correlate with social deficits and restricted neuronal loss in an environmental model of autism. *The International Journal of Neuropsychopharmacology*, 21, 871–882. <https://doi.org/10.1093/ijnp/pyy043>
- Altman, J., & Sudarshan, K. (1975). Postnatal development of locomotion in the laboratory rat. *Animal Behaviour*, 23, 896–920. [https://doi.org/10.1016/0003-3472\(75\)90114-1](https://doi.org/10.1016/0003-3472(75)90114-1)
- Arango-Tobón, O. E., Guevara Solórzano, A., Orejarena Serrano, S. J., & Olivera-La Rosa, A. (2023). Social cognition and prosocial behavior in children with attention deficit hyperactivity disorder: A systematic review. *Healthcare (Basel)*, 11, 1366. <https://doi.org/10.3390/healthcare11101366>
- Bardgett, M. E., Davis, N. N., Schultheis, P. J., & Griffith, M. S. (2011). Ciproxifan, an H3 receptor antagonist, alleviates hyperactivity and cognitive deficits in the APP Tg2576 mouse model of Alzheimer's disease. *Neurobiology of Learning and Memory*, 95, 64–72. <https://doi.org/10.1016/j.nlm.2010.10.008>
- Biotteau, M., Albaret, J.-M., & Chaix, Y. (2020). Developmental coordination disorder. *Handbook of Clinical Neurology*, 174, 3–20. <https://doi.org/10.1016/B978-0-444-64148-9.00001-6>
- Blumberg, M. S., & Adolph, K. E. (2023). Infant action and cognition: What's at stake? *Trends in Cognitive Sciences*, 8, 696–698. <https://doi.org/10.1016/j.tics.2023.05.008>
- Blumberg, M. S., Dooley, J. C., & Tiriack, A. (2022). Sleep, plasticity, and sensory neurodevelopment. *Neuron*, 110, 3230–3242. <https://doi.org/10.1016/j.neuron.2022.08.005>
- Brown, C. O., Uy, J., & Singh, K. K. (2020). A mini-review: Bridging the gap between autism spectrum disorder and pain comorbidities. *Canadian Journal of Pain-Revue Canadienne De La Douleur*, 4, 37–44. <https://doi.org/10.1080/24740527.2020.1775486>
- Brown-Lum, M., Izadi-Najafabadi, S., Oberlander, T. F., Rauscher, A., & Zwicker, J. G. (2020). Differences in white matter microstructure among children with developmental coordination disorder. *JAMA Network Open*, 3, e201184. <https://doi.org/10.1001/jamanetworkopen.2020.1184>
- Caligiore, D., Pezzulo, G., Baldassarre, G., Bostan, A. C., Strick, P. L., Doya, K., Helmich, R. C., Dirks, M., Houk, J., Jörntell, H., Lago-Rodriguez, A., Galea, J. M., Miall, R. C., Popa, T., Kishore, A., Verschure, P. F. M. J., Zucca, R., & Herreros, I. (2017). Consensus paper: Towards a systems-level view of cerebellar function: The interplay between cerebellum, basal ganglia, and cortex. *Cerebellum*, 16, 203–229. <https://doi.org/10.1007/s12311-016-0763-3>
- Canu, M.-H., Fourneau, J., Coq, J. O., Dannhoffer, L., Cieniewski-Bernard, C., Stevens, L., Bastide, B., & Dupont, E. (2019). Interplay between hypoactivity, muscle properties and motor command: How to escape the vicious deconditioning

- circle? *Annals of Physical and Rehabilitation Medicine*, 62, 122–127. <https://doi.org/10.1016/j.rehab.2018.09.009>
- Canu, M.-H., Montel, V., Dereumetz, J., Marqueste, T., Decherchi, P., Coq, J.-O., Dupont, E., & Bastide, B. (2022). Early movement restriction deteriorates motor function and soleus muscle physiology. *Experimental Neurology*, 347, 113886. <https://doi.org/10.1016/j.expneurol.2021.113886>
- Cazalets, J. R., Menard, I., Crémieux, J., & Clarac, F. (1990). Variability as a characteristic of immature motor systems: An electromyographic study of swimming in the newborn rat. *Behavioural Brain Research*, 40, 215–225. [https://doi.org/10.1016/0166-4328\(90\)90078-S](https://doi.org/10.1016/0166-4328(90)90078-S)
- Chinello, A., Di Gangi, V., & Valenza, E. (2016). Persistent primary reflexes affect motor acts: Potential implications for autism spectrum disorder. *Research in Developmental Disabilities*, 16, 30154–30158.
- Clarac, F., Vinay, L., Cazalets, J.-R., Fady, J.-C., & Jamon, M. (1998). Role of gravity in the development of posture and locomotion in the neonatal rat. *Brain Research Reviews*, 28, 35–43. [https://doi.org/10.1016/S0165-0173\(98\)00024-1](https://doi.org/10.1016/S0165-0173(98)00024-1)
- Coleman, R., Piek, J. P., & Livesey, D. J. (2001). A longitudinal study of motor ability and kinaesthetic acuity in young children at risk of developmental coordination disorder. *Human Movement Science*, Development coordination disorder: Diagnosis, description, processes and treatment, 20, 95–110. [https://doi.org/10.1016/S0167-9457\(01\)00030-6](https://doi.org/10.1016/S0167-9457(01)00030-6)
- Coq, J. O., Kochmann, M., Lacerda, D. C., Khalki, H., Delcour, M., Toscano, A. E., Cayetanot, F., Canu, M.-H., Barbe, M. F., & Tsuji, M. (2020). From cerebral palsy to developmental coordination disorder: Development of preclinical rat models corresponding to recent epidemiological changes. *Annals of Physical and Rehabilitation Medicine*, 63, 422–430. <https://doi.org/10.1016/j.rehab.2019.10.002>
- Coq, J. O., Strata, F., Russier, M., Safadi, F. F., Merzenich, M. M., Byl, N. N., & Barbe, M. F. (2008). Impact of neonatal asphyxia and hind limb immobilization on musculoskeletal tissues and S1 map organization: Implications for cerebral palsy. *Experimental Neurology*, 210, 95–108. <https://doi.org/10.1016/j.expneurol.2007.10.006>
- Cossart, R., & Khazipov, R. (2022). How development sculpts hippocampal circuits and function. *Physiological Reviews*, 102, 343–378. <https://doi.org/10.1152/physrev.00044.2020>
- Del Arco, A., Ronzoni, G., & Mora, F. (2011). Prefrontal stimulation of GABA(a) receptors counteracts the corticolimbic hyperactivity produced by NMDA antagonists in the prefrontal cortex of the rat. *Psychopharmacology*, 214, 525–536. <https://doi.org/10.1007/s00213-010-2055-9>
- Delcour, M., Massicotte, V., Russier, M., Bras, H., Peyronnet, J., Canu, M.-H., Cayetanot, F., Barbe, M. F., & Coq, J. O. (2018). Early movement restriction leads to enduring disorders in muscle and locomotion. *Brain Pathology*, 28, 889–901. <https://doi.org/10.1111/bpa.12594>
- Delcour, M., Olivier, P., Chambon, C., Pansiot, J., Russier, M., Liberge, M., Xin, D., Gestreau, C., Alescio-Lautier, B., Gressens, P., Verney, C., Barbe, M. F., Baud, O., & Coq, J. O. (2012). Neuroanatomical, sensorimotor and cognitive deficits in adult rats with white matter injury following prenatal ischemia. *Brain Pathology*, 22, 1–16. <https://doi.org/10.1111/j.1750-3639.2011.00504.x>
- Delcour, M., Russier, M., Amin, M., Baud, O., Paban, V., Barbe, M. F., & Coq, J. O. (2012). Impact of prenatal ischemia on behavior, cognitive abilities and neuroanatomy in adult rats with white matter damage. *Behavioural Brain Research*, 232, 233–244. <https://doi.org/10.1016/j.bbr.2012.03.029>
- Delcour, M., Russier, M., Castets, F., Turle-Lorenzo, N., Canu, M.-H., Cayetanot, F., Barbe, M. F., & Coq, J. O. (2018). Early movement restriction leads to maladaptive plasticity in the sensorimotor cortex and to movement disorders. *Scientific Reports*, 8, 16328. <https://doi.org/10.1038/s41598-018-34312-y>
- Dieu-Lugon, B. L., Dupré, N., Legouez, L., Leroux, P., Gonzalez, B. J., Marret, S., Leroux-Nicollet, I., & Cleren, C. (2020). Why considering sexual differences is necessary when studying encephalopathy of prematurity through rodent models. *European Journal of Neuroscience*, 52, 2560–2574. <https://doi.org/10.1111/ejn.14664>
- Dooley, J. C., Sokoloff, G., & Blumberg, M. S. (2021). Movements during sleep reveal the developmental emergence of a cerebellar-dependent internal model in motor thalamus. *Current Biology*, 31, 5501–5511.e5. <https://doi.org/10.1016/j.cub.2021.10.014>
- Du, W., Wilmut, K., & Barnett, A. L. (2015). Level walking in adults with and without developmental coordination disorder: An analysis of movement variability. *Human Movement Science*, 43, 9–14. <https://doi.org/10.1016/j.humov.2015.06.010>
- Eacott, M. J., & Norman, G. (2004). Integrated memory for object, place, and context in rats: A possible model of episodic-like memory? *The Journal of Neuroscience*, 24, 1948–1953. <https://doi.org/10.1523/JNEUROSCI.2975-03.2004>
- Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, 30, 123–152. <https://doi.org/10.1146/annurev.neuro.30.051606.094328>
- Eigsti, I.-M., Rosset, D., Col Cozzari, G., da Fonseca, D., & Deruelle, C. (2015). Effects of motor action on affective preferences in autism spectrum disorders: Different influences of embodiment. *Developmental Science*, 18, 1044–1053. <https://doi.org/10.1111/desc.12278>
- Einspieler, C., Peharz, R., & Marschik, P. B. (2016). Fidgety movements – Tiny in appearance, but huge in impact. *Jornal de Pediatria*, 92, S64–S70. <https://doi.org/10.1016/j.jpmed.2015.12.003>
- Einspieler, C., Sigafos, J., Bölte, S., Bratl-Pokorny, K. D., Landa, R., & Marschik, P. B. (2014). Highlighting the first 5 months of life: General movements in infants later diagnosed with autism spectrum disorder or Rett syndrome. *Research in Autism Spectrum Disorder*, 8, 286–291. <https://doi.org/10.1016/j.rasd.2013.12.013>
- Gabbard, C., & Bobbio, T. (2011). The inability to mentally represent action may be associated with performance deficits in children with developmental coordination disorder. *International Journal of Neuroscience*, 121, 113–120. <https://doi.org/10.3109/00207454.2010.535936>
- Geertsens, S. S., Willerslev-Olsen, M., Lorentzen, J., & Nielsen, J. B. (2017). Development and aging of human spinal cord circuitries. *Journal of Neurophysiology*, 118, 1133–1140. <https://doi.org/10.1152/jn.00103.2017>
- Gill, K. K., Rajan, J. R. S., Goldowitz, D., & Zwicker, J. G. (2020). Using a mouse model to gain insights into developmental

- coordination disorder. *Genes, Brain, and Behavior*, 19, e12647. <https://doi.org/10.1111/gbb.12647>
- Glanz, R. M., Dooley, J. C., Sokoloff, G., & Blumberg, M. S. (2021). Sensory coding of limb kinematics in motor cortex across a key developmental transition. *The Journal of Neuroscience*, 41, 6905–6918. <https://doi.org/10.1523/JNEUROSCI.0921-21.2021>
- Glanz, R., Sokoloff, G., & Blumberg, M.S. (2023) Cortical Representation of Movement Across the Developmental Transition to Continuous Neural Activity. *bioRxiv*, 2023.01.22.525085. <https://doi.org/10.1101/2023.01.22.525085>
- Gomez, A., & Sirigu, A. (2015). Developmental coordination disorder: Core sensori-motor deficits, neurobiology and etiology. *Neuropsychologia*, Special Issue: Sensory Motor Integration, 79(Part B), 272–287. <https://doi.org/10.1016/j.neuropsychologia.2015.09.032>
- Gramsbergen, A. (2001). Normal and abnormal development of motor behavior: Lessons from experiments in rats. *Neural Plasticity*, 8, 17–29. <https://doi.org/10.1155/NP.2001.17>
- Hadders-Algra, M. (2018). Neural substrate and clinical significance of general movements: An update. *Developmental Medicine and Child Neurology*, 60, 39–46. <https://doi.org/10.1111/dmcn.13540>
- Haida, O., Al Sagheer, T., Balbous, A., Francheteau, M., Matas, E., Soria, F., Fernagut, P. O., & Jaber, M. (2019). Sex-dependent behavioral deficits and neuropathology in a maternal immune activation model of autism. *Translational Psychiatry*, 9, 124. <https://doi.org/10.1038/s41398-019-0457-y>
- Hellewell, S. C., Yan, E. B., Agyapomaa, D. A., Bye, N., & Morganti-Kossmann, M. C. (2010). Post-traumatic hypoxia exacerbates brain tissue damage: Analysis of axonal injury and glial responses. *Journal of Neurotrauma*, 27, 1997–2010. <https://doi.org/10.1089/neu.2009.1245>
- Kalueff, A. V., Stewart, A. M., Song, C., Berridge, K. C., Graybiel, A. M., & Fentress, J. C. (2016). Neurobiology of rodent self-grooming and its value for translational neuroscience. *Nature Reviews Neuroscience*, 17, 45–59. <https://doi.org/10.1038/nrn.2015.8>
- Kashuk, S. R., Williams, J., Thorpe, G., Wilson, P. H., & Egan, G. F. (2017). Diminished motor imagery capability in adults with motor impairment: An fMRI mental rotation study. *Behavioural Brain Research*, 334, 86–96. <https://doi.org/10.1016/j.bbr.2017.06.042>
- Kempert, H., Nelson, L., & Heines, R. (2019). Clinical observations of adolescent chronic pain with coordination difficulties: Physical and psychosocial implications. *Pediatric Pain*, 21, 40–48.
- Khalki, H., Khalki, L., Aboufatima, R., Ouachrif, A., Mountassir, M., Benharref, A., & Chait, A. (2012). Prenatal exposure to tobacco extract containing nicotinic alkaloids produces morphological and behavioral changes in newborn rats. *Pharmacology Biochemistry and Behavior*, 101, 342–347. <https://doi.org/10.1016/j.pbb.2012.01.020>
- Luhmann, H. J., & Khazipov, R. (2017). Neuronal activity patterns in the developing barrel cortex. *Neuroscience*, 368, 256–267. <https://doi.org/10.1016/j.neuroscience.2017.05.025>
- Marks, W. N., Parker, M. E., & Howland, J. G. (2018). Chapter 7 - Variants of the Spontaneous Recognition Procedure Assessing Multisensory Integration Reveal Behavioral Alterations in Rodent Models of Psychiatric and Neurological Disorders. In A. Ennaceur & M. A. de Souza Silva (Eds.), *Handbook of behavioral neuroscience, handbook of object novelty recognition* (pp. 125–137). Elsevier.
- Milburn, A. (1973). The early development of muscle spindles in the rat. *Journal of Cell Science*, 12, 175–195. <https://doi.org/10.1242/jcs.12.1.175>
- Mirza, M. A., Ritzel, R., Xu, Y., McCullough, L. D., & Liu, F. (2015). Sexually dimorphic outcomes and inflammatory responses in hypoxic-ischemic encephalopathy. *Journal of Neuroinflammation*, 12, 32. <https://doi.org/10.1186/s12974-015-0251-6>
- Molnár, Z., Luhmann, H. J., & Kanold, P. O. (2020). Transient cortical circuits match spontaneous and sensory-driven activity during development. *Science*, 370, eabb2153. <https://doi.org/10.1126/science.abb2153>
- Mumby, D. G., Tremblay, A., Lecluse, V., & Lehmann, H. (2005). Hippocampal damage and anterograde object-recognition in rats after long retention intervals. *Hippocampus*, 15, 1050–1056. <https://doi.org/10.1002/hipo.20122>
- Ohshima, M., Coq, J. O., Otani, K., Hattori, Y., Ogawa, Y., Sato, Y., Harada-Shiba, M., Ihara, M., & Tsuji, M. (2016). Mild intra-uterine hypoperfusion reproduces neurodevelopmental disorders observed in prematurity. *Scientific Reports*, 6, 39377. <https://doi.org/10.1038/srep39377>
- Paquet, A., Olliac, B., Golse, B., & Vaivre-Douret, L. (2019). Nature of motor impairments in autism spectrum disorder: A comparison with developmental coordination disorder. *Journal of Clinical and Experimental Neuropsychology*, 41, 1–14. <https://doi.org/10.1080/13803395.2018.1483486>
- Parron, C., Poucet, B., & Save, E. (2004). Entorhinal cortex lesions impair the use of distal but not proximal landmarks during place navigation in the rat. *Behavioural Brain Research*, 154, 345–352. <https://doi.org/10.1016/j.bbr.2004.03.006>
- Petrosini, L., Picerni, E., Termine, A., Fabrizio, C., Laricchiuta, D., & Cutuli, D. (2022). The cerebellum as an embodying machine. *The Neuroscientist*, 30, 229–246. <https://doi.org/10.1177/10738584221120187>
- Phagava, H., Muratori, F., Einspieler, C., Maestro, S., Apicella, F., Guzzetta, A., Prechtl, H. F. R., & Cioni, G. (2008). General movements in infants with autism spectrum disorders. *Georgian Medical News*, 156, 100–105.
- Pires, V. A., Pamplona, F. A., Pandolfo, P., Fernandes, D., Prediger, R. D. S., & Takahashi, R. N. (2009). Adenosine receptor antagonists improve short-term object-recognition ability of spontaneously hypertensive rats: A rodent model of attention-deficit hyperactivity disorder. *Behavioural Pharmacology*, 20, 134–145. <https://doi.org/10.1097/FBP.0b013e32832a80bf>
- R Core Team. (2021). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.
- Rahi, V., & Kumar, P. (2021). Animal models of attention-deficit hyperactivity disorder (ADHD). *International Journal of Developmental Neuroscience*, 81, 107–124. <https://doi.org/10.1002/jdn.10089>
- Rinat, S., Izadi-Najafabadi, S., & Zwicker, J. G. (2020). Children with developmental coordination disorder show altered functional connectivity compared to peers. *NeuroImage: Clinical*, 27, 102309. <https://doi.org/10.1016/j.nicl.2020.102309>
- Rodda, J. M., Graham, H. K., Carson, L., Galea, M. P., & Wolfe, R. (2004). Sagittal gait patterns in spastic diplegia. *Journal of Bone and Joint Surgery. British Volume (London)*, 86, 251–258.

- Rose, S. A., Feldman, J. F., Jankowski, J. J., & Van Rossem, R. (2011). The structure of memory in infants and toddlers: An SEM study with full-terms and preterms. *Developmental Science*, *14*, 83–91. <https://doi.org/10.1111/j.1467-7687.2010.00959.x>
- Rouleau, N., & Reduron, L. (2020). Le trouble déficit de l'attention/hyperactivité. In *Traité de neuropsychologie de l'enfant* (Second ed.) (pp. 242–259). De Boeck Supérieur.
- Schmahmann, J. D. (2019). The cerebellum and cognition. *Neuroscience Letters*, *688*, 62–75. <https://doi.org/10.1016/j.neulet.2018.07.005>
- Smits-Engelsman, B., Bonney, E., & Ferguson, G. (2020). Motor skill learning in children with and without developmental coordination disorder. *Human Movement Science*, *74*, 102687. <https://doi.org/10.1016/j.humov.2020.102687>
- Smits-Engelsman, B. C. M., & Wilson, P. H. (2013). Noise, variability, and motor performance in developmental coordination disorder. *Developmental Medicine & Child Neurology*, *55*, 69–72. <https://doi.org/10.1111/dmcn.12311>
- Strata, F., Coq, J. O., Byl, N., & Merzenich, M. M. (2004). Effects of sensorimotor restriction and anoxia on gait and motor cortex organization: Implications for a rodent model of cerebral palsy. *Neuroscience*, *129*, 141–156. <https://doi.org/10.1016/j.neuroscience.2004.07.024>
- Sturman, O., Germain, P.-L., & Bohacek, J. (2018). Exploratory rearing: A context- and stress-sensitive behavior recorded in the open-field test. *Stress*, *21*, 443–452. <https://doi.org/10.1080/10253890.2018.1438405>
- Turano, A., Osborne, B. F., & Schwarz, J. M. (2019). Sexual differentiation and sex differences in neural development. *Current Topics in Behavioral Neurosciences*, *43*, 69–110. [https://doi.org/10.1007/7854\\_2018\\_56](https://doi.org/10.1007/7854_2018_56)
- Vaivre-Douret, L., Lalanne, C., & Golse, B. (2016). Developmental coordination disorder, an umbrella term for motor impairments in children: Nature and co-morbid disorders. *Frontiers in Psychology*, *7*, e502. <https://doi.org/10.3389/fpsyg.2016.00502>
- Valagussa, G., Trentin, L., Signori, A., & Grossi, E. (2018). Toe walking assessment in autism Spectrum disorder subjects: A systematic review. *Autism Research*, *11*, 1404–1415. <https://doi.org/10.1002/aur.2009>
- Vilensky, J. A., Damasio, A. R., & Maurer, R. G. (1981). Gait disturbances in patients with autistic behavior: A preliminary study. *Archives of Neurology*, *38*, 646–649. <https://doi.org/10.1001/archneur.1981.00510100074013>
- Warburton, E. C. (2018). Chapter 13 - Using the Spontaneous Object Recognition Memory Tasks to Uncover the Neural Circuitry of Recognition Memory: The Importance of Thalamic Nuclei. In A. Ennaceur & M. A. de Souza Silva (Eds.), *Handbook of behavioral neuroscience, handbook of object novelty recognition* (pp. 197–203). Elsevier.
- Wilson, P. H., Smits-Engelsman, B., Caeyenberghs, K., Steenbergen, B., Sugden, D., Clark, J., Mumford, N., & Blank, R. (2017). Cognitive and neuroimaging findings in developmental coordination disorder: New insights from a systematic review of recent research. *Developmental Medicine and Child Neurology*, *59*, 1117–1129. <https://doi.org/10.1111/dmcn.13530>
- Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal-neocortical interactions. *Neuropsychologia*, *48*, 2339–2356. <https://doi.org/10.1016/j.neuropsychologia.2010.04.016>
- Zhang, J.-M., Konkle, A. T. M., Zup, S. L., & McCarthy, M. M. (2008). Impact of sex and hormones on new cells in the developing rat hippocampus: A novel source of sex dimorphism? *The European Journal of Neuroscience*, *27*, 791–800. <https://doi.org/10.1111/j.1460-9568.2008.06073.x>
- Zuk, L. (2011). Fetal and infant spontaneous general movements as predictors of developmental disabilities. *Developmental Disabilities Research Reviews*, *17*, 93–101. <https://doi.org/10.1002/ddrr.1104>
- Zwicker, J. G., Missiuna, C., Harris, S. R., & Boyd, L. A. (2012). Developmental coordination disorder: A review and update. *European Journal of Paediatric Neurology*, *16*, 573–581. <https://doi.org/10.1016/j.ejpn.2012.05.005>

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